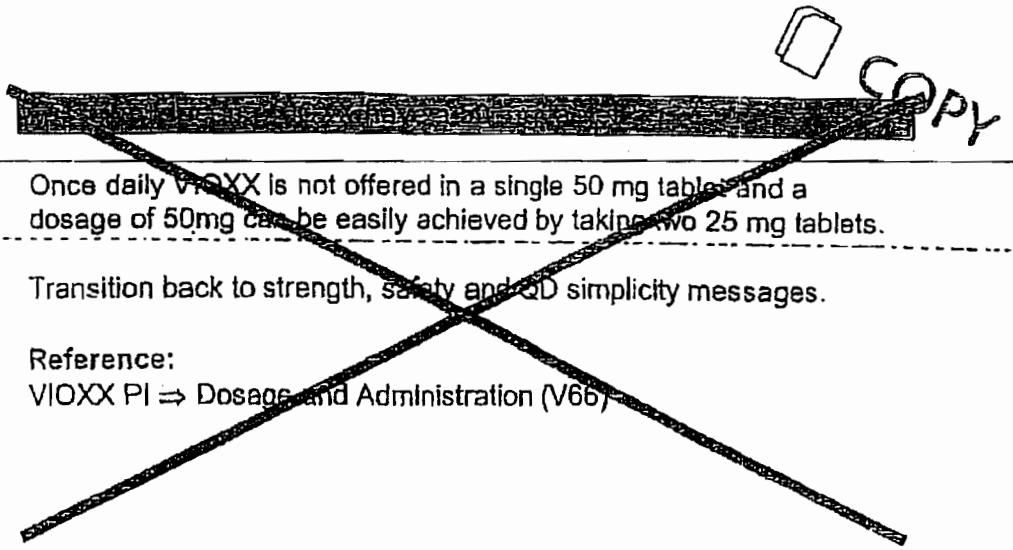


Once daily VIOXX is not offered in a single 50 mg tablet and a dosage of 50mg can be easily achieved by taking two 25 mg tablets.

Transition back to strength, safety and QD simplicity messages.

Reference:
VIOXX PI ⇒ Dosage and Administration (V66)

[redacted]

COPY

Doctor, the catalog price for once daily VIOXX is $2.02 for both 12.5 mg and 25 mg, offering your patients one of the best values available.

The catalog price for celecoxib is $2.38 for 100mg bid and $2.02 for 200 mg qd.

The catalog price for VIOXX 12.5 and 25mg is less expensive than the catalog prices for the usual daily doses of Arthrotec, Relafen, Daypro, and Voltaren.

In addition, the catalog price for the oral suspension of once daily VIOXX is competitive with other NSAIDs at $3.00.

This price comparison does not establish that products have comparable efficacy. These prices reflect direct cost and do not reflect actual costs paid by consumers.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

(For your reference, the average wholesale price (AWP) for once daily VIOXX is $2.42 for both 12.5 mg and 25 mg. AWP for celecoxib is $2.86 for 100 mg BID and $2.42 for 200 mg qd.
AWP for the oral suspension of once daily VIOXX is competitive with other NSAIDs at $3.60.)

Exhibit A - Part 3

[redacted] COPY

The 17 hour half-life of once daily VIOXX is entirely consistent with its once daily dosing. In all OA studies, lasting from 6 to 86 weeks with 3900 patients, once daily treatment with VIOXX 12.5 and 25 mg in the morning was associated with a significant reduction in joint stiffness upon first awakening in the morning. At doses of 12.5 and 25 mg once daily, the effectiveness of once daily VIOXX was shown to be comparable to ibuprofen 800mg TID and diclofenac 50 mg TID.

If probed further on half life:
Doctor, many drugs with half-lives shorter than 24 hour are effective when dosed once a day, for example Singulair, Prinivil, and Zocor.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Pharmacology ⇒ Excretion (V8)
VIOXX PI ⇒ Clinical Studies ⇒ OA (V16)
SINGULAIR® PI ⇒ Clinical Pharmacology ⇒ Excretion
PRINIVIL® PI ⇒ Clinical Pharmacology ⇒ Excretion
ZOCOR® PI ⇒ Clinical Pharmacology ⇒ Excretion

[redacted]

or

[redacted]

Doctor, you are correct when you say that COZAAR is metabolized by cytochrome P450 enzymes. COZAAR has been evaluated for safety in more than 3300 patients treated for hypertension. The overall incidence of adverse experiences reported with COZAAR in clinical studies was similar to placebo. No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine, and phenobarbital. COZAAR has been extensively used in clinical practice and clinical study settings for over four years with millions of patients treated. Clinical experience with COZAAR is well documented.

In vitro studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its active metabolite. Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined.

Celecoxib is metabolized by P450 2C9 and is an inhibitor of P450 2D6. The package circular states that the co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution. It also states that there is a potential for an in vivo drug interaction with drugs that are metabolized by P450 2D6.

Doctor, let me also note that VIOXX is not primarily metabolized by cytochrome P450 enzymes and is not known to inhibit enzymes of P450.
If you have additional questions regarding the P450 system and/or the implications for the products we discussed, I would be happy to submit a Professional Information Request to our Medical Services Department.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Pharmacology ⇒ Metabolism (V7)
COZAAR® PI ⇒ Clinical Pharmacology ⇒ General
COZAAR® PI ⇒ Adverse Reactions
COZAAR® PI ⇒ Precautions ⇒ Drug Interactions
Celecoxib PI ⇒ Precautions ⇒ Drug Interactions ⇒ General (C36)

Exhibit A - Part 3

[redacted]

COP

or

[redacted]

Doctor, you are correct when you say that ZOCOR is metabolized via CYP450. ZOCOR has been extensively used in clinical practice and clinical study settings for over 10 years with millions of patients treated and tens of thousands of patients studied in controlled trials. Clinical experience with ZOCOR is well documented.

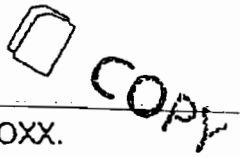
For ZOCOR, we know that the risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Certain drugs that inhibit this pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. Therefore, physicians contemplating concomitant therapy with ZOCOR and a drug that inhibits the P450 3A4 pathway should carefully weigh the potential benefits and risks of combined therapy and monitor for signs and symptoms of myopathy.

Celecoxib, on the other hand, is metabolized by P450 2C9 and is an inhibitor of P450 2D6. The package circular states that the co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution. It also states that there is a potential for an in vivo drug interaction with drugs that are metabolized by P450 2D6.

Doctor, let me also note that VIOXX is not primarily metabolized by the P450 system and is not known to inhibit the P450 system.

If you have additional questions regarding the P450 system and/or the implications for the products we discussed, I would be happy to submit a Professional Information Request to our Medical Services Department.

Exhibit A - Part 3



Transition back to the HI COXIB or HI NSAID messages for VIOXX.

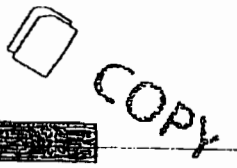
Reference:

VIOXX PI ⇒ Clinical Pharmacology ⇒ Metabolism (V7)

ZOCOR® PI ⇒ Warnings ⇒ Myopathy caused by drug interactions

Celecoxib PI ⇒ Clinical Pharmacology ⇒ Metabolism (C8)

Exhibit A - Part 3



[redacted]

Clarify: Which pain study are you referring to and why do you feel it was not well designed?

- **If the physician is concerned about the head-to-head study comparing VIOXX to Celebrex, offer to submit a PIR.**

- **If the physician is concerned because VIOXX was compared to 400 mg Ibuprofen, use the response offered in obstacle #10 in the Obstacle Response Guide and respond:**

To obtain an indication for the management of acute pain in adults, a drug must be studied in standard pain models as defined by the FDA. As it states in the ibuprofen PI, in clinical studies using doses of ibuprofen greater than 400mg are no more effective than the 400 mg dose in analgesia. Also, the maximum recommended dose of naproxen for analgesia is 550 mg.

In acute analgesic models of post-orthopedic surgical pain, post-operative dental pain and primary dysmenorrhea, once daily VIOXX relieved pain that was rated by patients as moderate to severe. In post-surgical dental pain studies, the onset of action with a single 50mg dose of once daily VIOXX occurred within 45 minutes.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Studies ⇒ Analgesia (V17)

- **If the physician is concerned about the different dosing regimens, respond:**

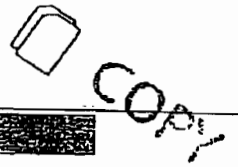
Doctor, this is a single dose model. It is a standard model designed to assess the analgesic effect of an agent. It was not designed to compare the dosing regimens of the agents, in this

instance, once daily VIOXX versus 3 times a day Ibuprofen or twice daily naproxen. However, it does demonstrate the relative efficacy of the two agents on onset of action, peak effect, and total pain relief over 8 hours. On the measures, once daily VIOXX was generally similar to the comparator NSAIDs.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Studies ⇒ Analgesia (V17)

Exhibit A - Part 3



[redacted]

Clarify: What specific hepatic effects are you concerned about?

If physician is concerned about liver function testing (LFTs), respond:
In controlled clinical trials of VIOXX, the incidence of borderline elevations of liver tests at doses of 12.5 and 25 mg daily was comparable to the incidence observed with ibuprofen and lower than that observed with diclofenac. In placebo-controlled trials, approximately 0.5% of patients taking once daily VIOXX 12.5 or 25 mg and 0.1% of patients taking placebo had notable elevations of ALT or AST. A patient who has an abnormal liver test while on once daily VIOXX should be monitored carefully for evidence of a more severe hepatic reaction.

Use of VIOXX is not recommended in patients with moderate or severe hepatic insufficiency.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

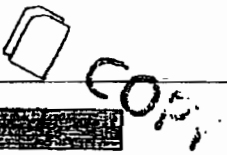
Reference:
VIOXX PI ⇒ Precautions ⇒ Hepatic Effects (V32)

If physician is concerned about metabolism, respond:
Doctor, metabolism of once daily VIOXX is primarily mediated through reduction by cystolic enzymes in the liver. It is not primarily metabolized by the P450 system and is not known to inhibit the P450 system in the liver.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Pharmacology ⇒ Metabolism (V7)

Exhibit A - Part 3



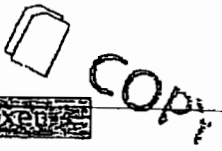
[redacted]

Doctor, as stated in the prescribing information, once daily VIOXX can be used concomitantly with ACE inhibitors. All NSAIDs may diminish the antihypertensive effect of ACE inhibitors. The prescribing information for once daily VIOXX states "In patients with mild to moderate hypertension, administration of 25 mg daily of VIOXX with the ACE inhibitor benazepril, 10 to 40 mg for 4 weeks, was associated with an average increase in mean arterial pressure of about 3 mm Hg compared to ACE inhibitor alone." Remember, all NSAIDs may diminish the antihypertensive effect of ACE inhibitors. Therefore, this effect is not unique to VIOXX.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Drug Interactions ⇒ ACE inhibitors (V40)

Exhibit A - Part 3



[redacted]

Clarify:

Doctor, why do you say that?

If the physician replies "It states in your product circular that VIOXX 50mg once daily was comparable to naproxen 550mg. This would seem to indicate that you are not comparable to 550mg bid," then respond:

Doctor, that statement is derived from single dose studies and is not intended to compare or draw conclusions about the efficacy of VIOXX or Anaprox over a 24 hour period. It was not designed to compare the dosing regimens of the agents. The single dose analgesia study was designed to compare time of onset, peak effect and total pain relief over 8 hours. In OA studies, once daily VIOXX 12.5mg and 25mg were comparable to ibuprofen 800mg tid and diclofenac 50mg tid. In each study, both 12.5mg and 25mg of VIOXX once daily were comparable to the comparator NSAIDs. Would you agree that 800 mg of ibuprofen tid and 50 mg of diclofenac tid were good NSAID comparators to demonstrate the efficacy of once daily VIOXX in OA over a full 24 hours? Will you try once daily VIOXX in your acute pain and OA patients?

If the physician replies "You only compared yourself to 550mg of naproxen in your pain studies" refer to the obstacle "The pain studies for VIOXX were not well designed" in the Obstacle Response Guide, #18.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

For Representatives background, naproxen sodium is Anaprox, and naproxen is Naprosyn.

[redacted] Copy

I would like to clarify that in general, once daily VIOXX is metabolized primarily through reduction by cytosolic enzymes in the liver, not primarily through the P450 system. Cytochrome P450 plays a minor role in the metabolism of once daily VIOXX.
The inhibition of P450 3A4 activity by administration of ketoconazole 400 mg daily did not affect the disposition of VIOXX. However, induction of general hepatic activity by administration of the non-specific inducer rifampin 600 mg daily produced a 50% decrease in VIOXX plasma concentrations.

If you are interested in further information on the metabolism of once daily VIOXX, I'd be happy to submit a PIR.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Pharmacology ⇒ Metabolism (V7)

Background Information
Cytochrome P450: Inhibition and Induction (referenced from the Analgesic and Anti-Inflammatory Training Program, Module 5, pages 31-32).

Inhibition
Inhibition of specific CYP450 enzymes can also affect the conversion of a drug to its active metabolite. Significant drug interactions may occur when NSAIDs that are metabolized through the CYP450 system are administered together with drugs that inhibit enzymes of the CYP450 systems. Concomitant administration of a drug with a known inhibitor of cytochrome P450 enzymes can alter the relative amounts of parent and metabolite that end up in the general circulation. For example, concomitant administration of fluconazole, a known inhibitor of CYP2C9, and celecoxib results in an increase in

Exhibit A - Part 3

celecoxib plasma concentrations due to the inhibition of celecoxib metabolism via CYP2C9 by fluconazole.

In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an in vivo drug interaction with drugs that are metabolized by CYP2D6. Some examples of drugs that are metabolized by CYP2D6 are certain antidepressants (e.g., tricyclic antidepressants (TCAs) and selective serotonin re-uptake inhibitors (SSRIs), antipsychotics (e.g., haloperidol), and narcotics (e.g., codeine). Coadministration of these agents with celecoxib may result in increased serum concentrations of these drugs.

Induction

Drug-drug interactions can also occur when one drug induces the metabolism of another by increasing the synthesis or reducing the degradation of CYP450 enzymes, as shown in Figure 13. In this case, the clearance of the drug will be increased and the pharmacological effects decreased. Increased synthesis of CYP450 protein (which leads to an increase in CYP450) activity) can be associated with exposure to certain drugs or environmental agents. Enzyme induction can lead to an increased rate of drug metabolism and corresponding decreases in the availability of the parent drug. For example, indinavir is metabolized by CYP3A4. Therefore, the drug rifampin, a potent inducer of CYP3A4, should not be co-administered because it may lead to markedly diminished plasma concentrations of indinavir.

[redacted]

Clarify:
What is your specific concern?

The physician may respond:
(A) "I am hesitant to use VIOXX in my patients because it may worsen CHF," or
(B) "VIOXX has the potential to increase the risk of MI."

Response to (A) "I am hesitant to use VIOXX in my patients because it may worsen CHF."
Doctor, as you know, there are precautions you should take when prescribing any NSAID for your patients with CHF. Because once daily VIOXX® is an NSAID, you should consider taking these same precautions when considering the use of once daily VIOXX® for this specific patient population.

Clinical trials with once daily VIOXX® 12.5 mg and 25 mg have shown renal effects such as hypertension and lower extremity edema similar to those observed with comparator NSAIDs. VIOXX® should be used with caution and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or edema.

(NOTE: If the physician asks about concomitant use with ACEIs, refer to Obstacle Response No. 20.)

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Renal Effects (V33)
VIOXX PI ⇒ Precautions ⇒ Fluid Retention and Edema (V35)

~~Response to (B) "VIOXX increases the risk of MI."~~

Doctor, once daily VIOXX has no effect on platelet aggregation, and therefore would not be expected to demonstrate reductions in MI or other CV events. Agents such as low-dose aspirin are routinely prescribed for CV patients for their effect on the inhibition of platelet aggregation. Therefore, once daily VIOXX® is not a substitute for aspirin for cardiovascular prophylaxis. However, once daily VIOXX 50 mg had no effect on the anti-platelet activity of low dose (81 mg daily) aspirin when the two were given together.

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(Refer to Obstacle Response No. 7.)

If probed further:
Offer to submit a PIR.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Aspirin (V41)

COPY

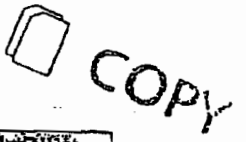
[redacted]

Doctor, It is important to note that the time period you refer to, 1 to 2 weeks, was the predetermined initial time intervals in the study at which pain relief was measured. Patient's pain relief was simply not assessed earlier than that by design. The objective of these trials (up to one year) was to evaluate study endpoints over the course of the trial-not onset of action. These were not studies of onset of action

If you would like specific information on the onset of action of once daily VIOXX in acute pain, let's look at the comparison to naproxen sodium (Anaprox) in dental pain which showed an onset of action of VIOXX 50 mg within 45 minutes.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI⇒Clinical Studies PI⇒OA (V16)
VIOXX PI⇒Clinical Pharmacology ⇒ Pharmacokinetics ⇒ Absorption (V4)
VIOXX PI⇒Clinical Studies□Analgesia, including Dysmenorrhea (V17)
Celecoxib PI⇒ Clinical Pharmacology ⇒ Pharmacokinetics ⇒ Absorption (C4)



[redacted]

Clarify: Dr. what specifically is your concern?

If the concern is with bleeding time (pre and post-operatively), respond:
Once daily VIOXX® has not been studied in a pre-operative setting. I cannot make a recommendation regarding pre-operative use.

In studies of healthy volunteers who had not undergone surgery, at multiple doses of up to 375 mg daily up to 12 days, VIOXX® had no effect on bleed time relative to placebo. Similarly, bleeding time was not altered in a single dose study with 500 or 1000mg of VIOXX®.

Additionally, VIOXX® 50 mg has shown no effect on platelet aggregation. Also, once daily VIOXX 50 mg had no effect on the anti-platelet activity of low dose (81 mg daily) aspirin when the two were given together.

If requesting further information, please submit a request.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

If the concern is the management of acute pain, post-operatively, respond:
In order to obtain an acute pain indication, VIOXX® was demonstrated to provide effective pain relief in 3 acute pain models.

Two of the pain models involved surgery – the post-orthopedic surgical model and the post-operative dental pain model. The post-orthopedic surgery studies involved patients with knee or hip replacement. Patients received their first dose of VIOXX®, on average, 46 hours after surgical procedure (range 17 to 97 hours). In our acute dental pain study, VIOXX® provided onset of pain relief within 45 minutes.

Exhibit A - Part 3

Dr., in contrast, Celebrex is not indicated for the management of acute pain.

If further information is requested, offer to submit a PIR.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Studies ⇒ Platelets (V21)

Exhibit A - Part 3

[redacted]

Clarify:
Doctor, specifically what safety concerns are you referring to?

If the physicians' concern is renal safety or edema:
Refer to obstacle # 12, 4

If the physicians' concern relates to hepatic effects or cardiovascular safety:
Refer to obstacle # 19,23

If the physicians' concern is whether the rate of ulcers increases over time when treating patients with VIOXX, respond with the following:

Doctor, In order to address your concerns, I would like to discuss the extensive GI endoscopy program that has been conducted for VIOXX®. In two identical, large trials, the **cumulative** incidence of ulcers with patients taking VIOXX 25 mg and 50 mg once daily (2 to 4X the dose used for osteoarthritis) was studied. The results with VIOXX showed significantly fewer endoscopic ulcers than with ibuprofen 2400 mg at weeks12 and 24. (Refer to VIOXX® PI, Clinical Trials.)

Doctor, I would like to bring to your attention a few important factors regarding our endoscopy study design:

First, "cumulative rates" include all patients who develop an ulcer up to a specified point in time. In other words, the rates shown at week 24 include all endoscopic ulcers detected by week 12 and all endoscopic ulcers detected between weeks 12 and 24. This method assures that patients developing ulcers at any time during the study are represented in the overall risk assessment.
As noted in the attached Laine reprint (page 780, second full paragraph), when refereneing the endoscopy trials for VIOXX®,

Exhibit A - Part 3

"Ulcer rates in the first 3 months of the study were not significantly different compared to the second three months in the rofecoxib groups or in the ibuprofen groups (4.1% vs. 5.5% in the 25 mg rofecoxib group, 7.3% vs. 7.4% in the rofecoxib 50 mg group, and 27.7% vs. 18.2% in the ibuprofen group)". Please refer to the Important Considerations for Endoscopy Studies as noted in the detail aid.

Please provide appropriate and referenced balancing throughout product discussions with healthcare professionals.

Note: We have heard reports from the field that Searle/Pfizer representatives are describing the results as "additive rates". Additive rates evaluate an increase over a specified period of time and make assumptions that rates continue to increase by the same rate into the future.

The rates reported in this study are not additive rates.

Exhibit A - Part 3

COPY

[redacted]

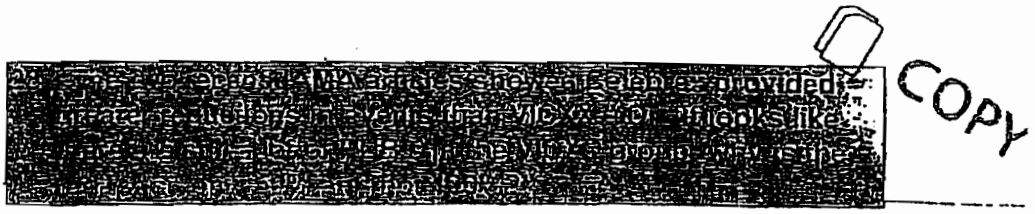
Dr., I can appreciate your concern. Let me clarify Merck's view of this and every other contraindication for our product.

The fact remains that a contraindication is just that – a contraindication. At no time will Merck ever suggest that you prescribe an agent to a patient who is contraindicated for its use.

As you know, use of hydrochlorothiazide in patients who are allergic to sulfonamides is contraindicated. Hyzaar, which is losartan plus hydrochlorothiazide, is contraindicated for use in patients with hypersensitivity to other sulfonamide-derived drugs. However, losartan, (Cozaar) alone is not contraindicated in these patients. We do not, have not, and never will recommend the use of Hyzaar for patients who have sulfonamide allergies. Cozaar is not contraindicated for patients who have a sulfonamide allergy and can be prescribed for these patients who need control of their BP.

Regarding the CoxIb class, **VIOXX does not have a contraindication for sulfonamide allergic patients** – Celebrex does.

(Note: If you have not already discussed Cozaar/Hyzaar with this physician on this call, take the opportunity to initiate a discussion regarding these products after you close your product discussion for VIOXX. One suggested transition may be, "Just as we have discussed appropriate patients to prescribe VIOXX for, I'd like to discuss appropriate patients for therapy with Cozaar, Hyzaar 50/12.5 and Hyzaar 100/25...")



Note: Physician is referring to the JAMA article, November 24, 1999 issue, Volume 282, No. 20

Representative Response:

Actually those were different types of studies. **(See below or in the cover bulletin for background information)**

The JAMA article on VIOXX is a combined analysis of PUBs, Perforation, symptomatic Ulcers and Bleeds from all 8 double bind, randomized phase 2b/3 OA trials. The Celebrex article, which is the information currently contained in their PI, is a prospective endoscopy trial with Celebrex, comparator NSAIDs and placebo. This is similar to the study I have been discussing with you from our package circular, which compares VIOXX to Ibuprofen, and placebo. The JAMA study on VIOXX was designed to compare VIOXX to the comparator NSAIDS, not placebo. No one knows what the background rate of PUBs in patients treated with placebo would be, but we know it is not zero.
It would be inaccurate to compare the JAMA articles on VIOXX and Celebrex because the endpoints (ulcers detected on surveillance endoscopy versus clinically significant events) are entirely different. Until head to head comparative trials are designed and completed, no conclusions can be drawn regarding relative GI safety between these agents.

Additional studies will need to be conducted to further support these conclusions. As stated in the VIOXX package insert (under the 044 endoscopy data), "the correlation between findings of endoscopic studies, and the relative incidence of clinically serious upper GI events that may be observed with different products, has not been fully established."

However, I can share with you information for VIOXX from our endoscopy trials. These results are listed in our package circular, in our detail aids and most recently were published in Gastroenterology. The lead author of the study was Dr. Loren Laine. Among 742 OA patients without ulcers on baseline endoscopy, the cumulative incidence of gastroduodenal ulcers ≥ 3mm with VIOXX (25 mg or 50 mg) was significantly ($p<0.001$) lower than ibuprofen.
Also, in controlled clinical trials summarized in our promotional literature, among 3357 patients who were treated with VIOXX 12.5 mg, 25 mg, and 50 mg, only (POB data):

- 2 of 3357 (0.06%) patients experienced a serious Clinical Upper GI event in the first 3 months
- and 4 of 3357 patients cumulative (0.12%) experienced a serious Clinical Upper GI event in the first 12 months.

Transition back to Laine reprint or detail aid to further discuss results with VIOXX and deliver Top 5 messages, provide appropriate balance and close the call.

Remember that you may not discuss or provide the JAMA article to your physicians. You must submit a PIR to address any additional concerns.

Background Information:

It is critical to understand the differences in the types of analyses that have been performed in the studies that are now being published in JAMA and Gastroenterology. Merck and Searle have both performed endoscopy studies comparing VIOXX® and celecoxib to NSAIDs. Both companies also have data from their combined clinical trials in their PIs describing what are termed "serious" upper GI events (Perforations, Obstructions and Bleeds, or POBs). These events are found during the course of clinical treatment, NOT during a scheduled endoscopy. In addition, Merck has just

published in JAMA the results of a PUB (Perforations, symptomatic Ulcers and Bleeds) analysis, data which is not in the PI for VIOXX®.

The first type of analysis is the endoscopy study. In this study patients are randomized to study drugs (or placebo) and undergo scheduled endoscopies (in the VIOXX® trials these were at baseline 6, 12, and 24 weeks). Ulcers that are seen through the endoscope are measured and counted. This provides a basis for comparing the effect of drugs on the gastric mucosa and is seen as a surrogate for clinically significant events, even if the ulcers seen are not symptomatic and do not actually lead to bleeding or other complications. This is the type of analysis done in the Laine paper published in Gastroenterology and the Searle paper in JAMA, data in the PIs for both VIOXX® and celecoxib.

It is sometimes considered more clinically relevant to compare drugs based on the number of clinical events that occur. Thus the second type of analysis is done, looking at events that occur during the trials. These occur at much lower rates than endoscopically visualized ulcers, so it requires many more patients to see any differences between drugs. Merck chose to measure PUBs (perforations, ulcers and bleeds) while the clinical event data in the PIs for VIOXX® and celecoxib measured POBs (perforations, obstructions and bleeds). The primary difference between these is the U – Ulcers that present due to clinical signs or symptoms. In the Merck JAMA paper, if any patient underwent endoscopy for cause (that is, the patient demonstrated symptoms that the physician judged worthy of follow-up) and ulcers were detected, these were included as events, along with the POBs. This explains why the rates of POBs in the PIs for celecoxib and VIOXX® are lower than the PUB rates shown in the JAMA paper on VIOXX®.

[redacted]

Doctor, it would have been great news for patients if Celebrex received an indication to prevent cancer, but what Celebrex actually received was an indication for a rare genetic disorder, familial adenomatous polyposis (FAP).

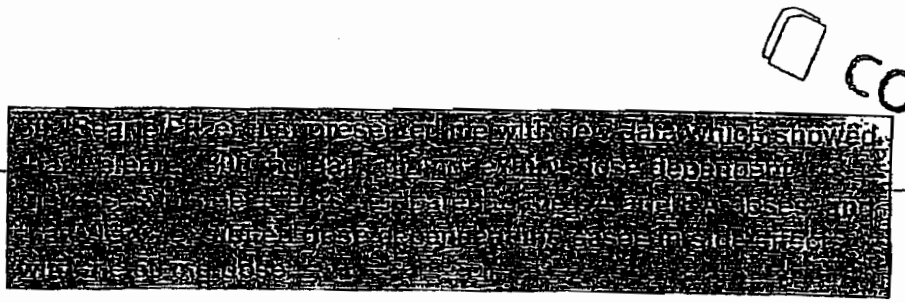
The indication is:

"to reduce the number of adenomatous polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care". The indication further states, "It is not know whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients." The label also states that "treatment with Celebrex in FAP has not been shown to reduce the risk gastrointestinal cancer or the need for prophylactic colectomy or other FAP –related surgeries."

If pressed about whether Merck is conducting studies state,

"Doctor, I am not permitted to discuss uses that not included in the labeling for VIOXX. If you would like, I can submit a request for information to our medical services department."

Transition back to the HI COXIB or HI NSAID messages for VIOXX using the following statement, "So you can see, doctor, this is a new indication for a very rare disorder. Let's discuss much more common disorder-OA."



Note: You may have to probe to uncover the real obstacle. It may be presented as one of the following:

- Celebrex is now proven to be safer than VIOXX.
- Celebrex is a safer agent.
- Are there safety issues with VIOXX?

CLARIFY FIRST:

"Doctor, what is your concern regarding VIOXX? Is there a particular area of concern you want to discuss?"

RESOLVE

Doctor, Searle/Pfizer may be using their new FAP data to suggest that Celebrex 400mg bid, the dose used in the FAP studies, had an adverse event profile "*similar to that reported for patients in arthritis controlled trials*". It is important to realize that the FAP study included 83 patients, who were generally younger and otherwise healthy. This is a population very different from the patient population of OA studies.

It is important to realize that VIOXX 50mg is the recommended dose for acute pain or analgesia, and not a recommended dose for OA. In fact, our product circular states,

"*Approximately one thousand patients were treated with VIOXX in analgesia studies. The adverse experience profile in the*

analgesia studies was generally similar to those reported in the osteoarthritis studies."

Doctor, what this means is that when the 50mg dose was used in analgesia studies, it had a similar adverse experience profile as that which was seen with VIOXX 12.5 and 25mg in osteoarthritis studies.

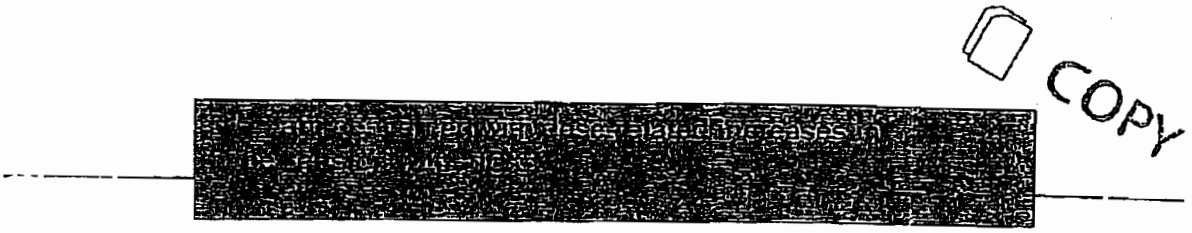
If the doctor refers to the increased incidence of edema or hypertension listed under the Adverse Experiences table:

Doctor, the data that you are referring to are from the use of VIOXX 50mg in two, 6-month, OA, endoscopy trials, which evaluated the GI safety of VIOXX. VIOXX 50mg is not a recommended dose for the treatment of OA, but was used in these studies to determine GI safety. VIOXX, at both 25 and 50mg doses, yielded significantly fewer endoscopic ulcers than ibuprofen. Let me reiterate that in analgesia studies with VIOXX 50mg, the incidence of hypertension and edema was similar to that reported in the OA studies with VIOXX12.5 and 25mg.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.

Exhibit A - Part 3



Clarify:

Doctor, what has led to your concern that VIOXX causes dose-related increases in hypertension?

Resolve:

Doctor, according to the product circular for VIOXX, the incidence of hypertension reported in OA studies, regardless of causality, was 3.5% with the 12.5 or 25mg dose. For patients who were treated with VIOXX 50mg in analgesia studies, the VIOXX product circular states,

> *"Approximately one thousand patients were treated with VIOXX in analgesia studies. The adverse experience profile in the analgesia studies was generally similar to those reported in the osteoarthritis studies."*

Doctor, what this means is that when the 50mg dose was used in analgesia studies, it had a similar adverse experience profile as that which was seen with VIOXX 12.5 and 25mg in OA studies. VIOXX 50mg is not a recommended dose for OA.

If the doctor refers to the increased incidence of hypertension listed under the Adverse Experiences table:

Doctor, the data that you are referring to is from the 6-month, OA, endoscopy trials, which were used to evaluate the GI safety of VIOXX. VIOXX 50mg is not a recommended dose for the treatment of OA, but was used in these studies to evaluate GI safety. VIOXX, at both 25 and 50mg doses yielded significantly fewer endoscopic

ulcers than ibuprofen. Let me reiterate that in analgesia studies with VIOXX 50mg, the incidence of hypertension was similar to that reported in the OA studies with VIOXX 12.5 and 25mg.

Doctor, have I addressed your concern with dose-related increases in hypertension with VIOXX?
Now let's talk about the benefits VIOXX offers you and your patients in the treatment of OA and acute pain.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.

Exhibit A - Part 3

COPY

The design of the studies differed in a number of significant respects and therefore the results of the two studies cannot be compared. So, let me tell you about the data for VIOXX from our OA clinical trials at the 12.5 mg and 25 mg doses.

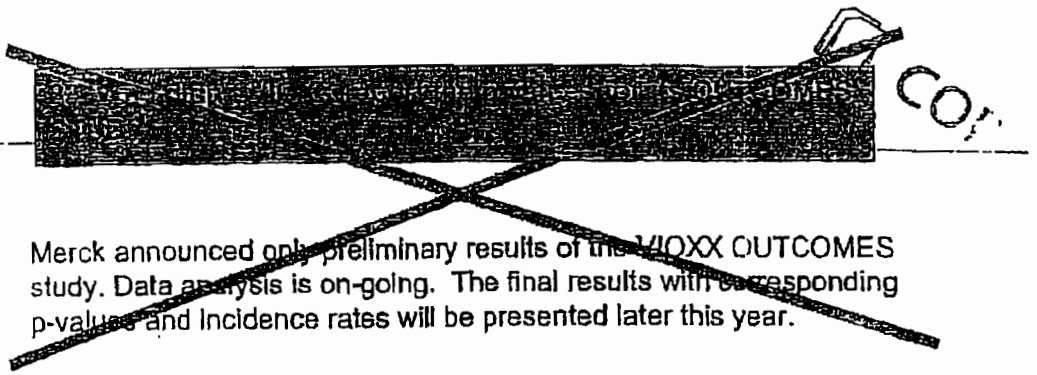
In an extensive review of all of our Phase III OA clinical trials, VIOXX did not show an increase in the incidence of thromboembolic events compared to placebo or the comparator NSAIDS.

You can feel confident that Merck has conducted OA clinical trials for VIOXX 12.5mg and 25mg daily in over 3600 patients with OA; approximately 1400 patients received VIOXX for 6 months or longer and approximately 800 patients for one year or longer. These trials included a placebo arm in the six week studies and two comparator NSAIDS, ibuprofen 2400 mg and diclofenac 150 mg daily. VIOXX 12.5mg and 25mg has shown to provide OA pain relief all day, all night and into the next morning.

Referring to the Adverse Events data, as listed in the package insert for VIOXX 12.5 mg and 25mg daily, the only Cardiovascular System adverse event experienced as occuring over 2% (in trials of six-weeks to six-months) was hypertension at 3.7 % vs. comparators of ibuprofen 2400 mg daily at 3.0% and diclofenac 150 mg daily at 1.6%. In addition, stroke and MI each occurred in less than 0.1% of patients taking VIOXX in our OA clinical program.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Note: If the physician has questions regarding the hypertension & edema rates for VIOXX, please refer to obstacles #19 & #12. Also, the Renal Card (OAN #001962(1)) is an excellent resource that has been developed to directly address issues pertaining to hypertension & edema.



Merck announced only preliminary results of the VIOXX OUTCOMES study. Data analysis is on-going. The final results with corresponding p-values and incidence rates will be presented later this year.

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[redacted]

Doctor, Mobic is a non-steroidal anti-inflammatory drug – an NSAID – that inhibits both COX-1 and COX-2 at its therapeutic doses. It does not selectively inhibit COX-2.

If the doctor continues and asks how Mobic differs from VIOXX, respond:

> Doctor, VIOXX is indicated for the signs and symptoms of OA, acute pain in adults, and primary dysmenorrhea. Mobic is indicated for OA. VIOXX is available in three tablet strengths, 12.5 mg, 25 mg, and 50 mg, which allows you to prescribe VIOXX one tablet, once daily for all indications. Mobic is available in a 7.5 mg tablet; to increase the dose requires two 7.5 mg tablets. Finally, the two OA doses of VIOXX – 12.5 mg and 25 mg – are priced the same. The highest dose of Mobic is twice as expensive as the lowest dose because patients must take two tablets.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Alternatively, if the doctor continues and asks how Mobic's mechanism of action that you just explained differs from that of VIOXX, respond:

> Doctor, VIOXX is an NSAID that inhibits COX-2 without inhibiting COX-1 at therapeutic doses. Of course, Doctor, we would not recommend that you base your prescribing decision on the mechanism of action of the drug. Can I take a minute and share with you the clinical data on the Strength, Safety, and QD Simplicity of VIOXX?

~~Transition back to the HI COXIB or HI NSAID messages for VIOXX.~~

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[redacted]

Doctor, if cost is your reason for considering Mobic, let me point out that Mobic is available only in a 7.5mg tablet. That means that if you need to increase your patients dose to 15mg, the maximum recommended dose for OA, your patients cost will double. In contrast, VIOXX 12.5 and 25 mg tablets are flat priced so you can select the appropriate dose for your OA patients without regard to cost.

Let me share with you the benefits that VIOXX can provide for you and your patients.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.

[redacted] COPY

Doctor, I can understand that experience with a medication is very important to you. The most valuable experience is not just what has happened abroad, but the clinical experience that you and your colleagues have developed on your own. What has been your experience with VIOXX over the last year? Have you been satisfied with your clinical experience using VIOXX over the last year?

In the last year, VIOXX has achieved a vast amount of clinical experience among many specialties-Rheumatologists, Orthopedic Surgeons, Gastroenterologists, Internists, and Primary Care Physicians. VIOXX has become second most prescribed branded NSAID in the U.S. in less than one year. Is this the kind of experience that is important to you?

Not only has VIOXX developed a tremendous amount of clinical experience within the U.S., but VIOXX has been extensively studied in clinical trials. Let me share some data with you demonstrating the safety and efficacy of VIOXX.

Transition back to the HI COXIB or HI NSAID messages for VIOXX. Be sure to emphasize the data within your Core Visual Aid as you deliver these messages. Focus on the number of patients within each study and the benefit which the results present for the doctor's patient.

Remember to provide appropriate balancing information as part of all product discussions.

Doctor, I can understand that when choosing a medication to treat your OA patients, you would want to choose a medication with a well documented GI safety and tolerability profile.

Doctor, the studies which you're referring to are not reflected in the prescribing information for MOBIC. I believe that those studies only lasted 28 days, did not include endoscopic data, and only included the 7.5mg dose of MOBIC.

Let me remind you of the extensive GI data available for VIOXX. In two studies involving over 1500 patients, VIOXX demonstrated significantly fewer endoscopic ulcers than ibuprofen and was consistent across all studies. These studies lasted 6 months, and the incidence rate of ulcers in groups receiving VIOXX did not increase over time. These studies were done with the 25mg and 50mg dose of VIOXX, although I want to remind you that the 25mg dose is the maximum recommended dose for chronic OA.

Does the duration and inclusion of endoscopy data in the VIOXX studies cause you to be more impressed with the data for VIOXX than that of MOBIC?

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.

COPY

[redacted]

Doctor, there are no head-to-head studies comparing the cardiovascular profile of the two drugs. As a result, you cannot compare the drugs and conclude that one drug had fewer events than the other. What you may be referring to is press reports of the incidence rates in two separate studies. In the VIOXX GI Outcomes Trial (VIGOR), the incidence of MI was 0.4% with VIOXX and 0.1% with naproxen. Upon further analysis, four percent of patients in the VIOXX GI Outcomes Study had experienced a cardiac event such as a heart attack or stroke before entering the study and thus met the established criteria for the use of aspirin for secondary CV prophylaxis. In the remaining 96% of patients for whom aspirin was not indicated for secondary CV prophylaxis, the incidence of MI was lower—0.2% for VIOXX and 0.1% for naproxen. This difference was not statistically significant.

In a separate GI outcomes trial of Celebrex, the CLASS study, Searle has reported that the incidence of MI was 0.5% with Celebrex, 0.3% with diclofenac, and 0.5% with ibuprofen. They also presented data for patients who were not prescribed aspirin. In this group, the incidence of MI was 0.2% for Celebrex and 0.1% for the comparator NSAIDs Again, doctor, I want to emphasize that the results of two different studies can't be compared, and that's particularly true here when you have studies of differing duration and in different patient populations.

If needed, continue to address the physicians concerns with the cardiovascular effects of VIOXX by guiding them through the Cardiovascular Card as outlined in Roadmap for the CV Card.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

NOTE: There will be an additional PIR to address these issues available shortly.

If the doctor asks you further for the incidence of MI from the OA studies presented in the package insert for VIOXX tell them,

In the clinical OA trials for VIOXX reported in our package insert, the incidence of MI was less than 0.1% with VIOXX.

If needed, continue to address the physicians concerns with the cardiovascular effects of VIOXX by guiding them through the Cardiovascular Card as outlined in Roadmap for the CV Card.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.